REMARKS

Claims 1-10, 12-13, 15-35, 49 and 51 are pending. Amendments to claims 1, 12, 14, 15, 16, and 49 have been made. Support for all amendments is found in applicants' specification as filed. For example, support for "filtering the multivesicular liposomal particle composition by cross-flow filtration" is found at page 25, lines 10-14. No new matter is introduced by these amendments.

The Claimed Invention

Applicants' claimed invention provides a well-defined processing method suitable for commercial scale manufacturing of Multi Vesicular Lipsomes (MVLs) in volume. The MVL can be produced according to an aseptic process, or can be subjected to non-destructive terminal sterilization. The method includes formation of a first emulsion of an aqueous phase and a solvent phase, the solvent phase containing amphipathic lipid and neutral lipid, emulsifying the first emulsion and another aqueous phase to form a second emulsion. The method also includes filtering of the resulting multivesicular liposomal particle composition, by cross flow filtration.

A relationship between the emulsion viscosity and the energy deposited into the emulsion to form it is established and exploited in the current invention. Increasing the mixing speed or time, and therefore increasing the energy deposited into the emulsion, allows greater accumulated shear, resulting in smaller first emulsion droplets. As the first emulsion particles decrease in size, the viscosity increases correspondingly. This allows reliable scale-up of processes from the bench to commercial scale.

The method produces an aqueous suspension of MVLs, having particle sizes in the micron and greater range, suitable for injection.

Rejection Under 35 U.S.C. §112

Claim 48 has been rejected as being indefinite. Applicants respectfully traverse the rejection as moot, as claim 48 has been cancelled.

Rejection Under 35 U.S.C. § 103(a) Over Kim et al. (Cancer Treatment Reports, v.71, pp 705-711, 1987), Assil et al. (Arch. Opthalmol., v.105, pp 400-403, 1987), Bonetti et al. (Cancer Chemother. Pharmacol., 1994), Kim et al. (United States Patent No. 5,723,147), or Sankaram et al. (United States Patent No. 5,766,627)

Claims 1-35, 48, 49 and 51 have been rejected as obvious over Kim et al. (1987), Assil et al., Bonetti et al., Kim et al. '147 or Sankaram et al. Applicants respectfully traverse the rejection for the following reasons. The prior art references cited for this rejection, taken individually or in any combination, fail to teach or suggest applicants' claimed invention to one of skill in the art. Each of these references employs a method for treating the product compositions, in order to effect conentration, removal of unencapsulated drug, or buffer exchange.

For example, in Kim et al. (1987), the "liposomes [are] then isolated by centrifugation at 600 X g for 5 minutes, and washed with phosphate-buffered saline ... thrice" (page 706, middle of left hand column, in Synthesis of Multivesicular Liposomes).

For example, in Assil et al., the procedure is stated as being a modification of Kim et al., in that "the mixture was then centrifuged at 500 g for ten minutes. To remove free drug, the supernatant was withdrawn and the liposomes were resuspended in phosphate-buffered saline solution... five times" (page 400, bottom of central column, in Materials and Methods).

For example, in Bonetti et al., "the Depo/methotrexate particles were then isolated by centrifugation at 600 X g for 5 min and washed thrice with 0.9% NaCl solution" (page 2, top of right hand column).

For example, in Kim et al. '147, the "liposomes were then isolated by centrifugation at 600 X g for 5 minutes; the supernatant was decanted, and the liposome pellet was resuspended in 5 ml of normal saline (0.9% sodium chloride). The liposomes were isolated again by centrifugation at 600 X g for 5 minutes" (col. 8, lines 50-54).

For example, in Sankaram et al., the "MVL were then isolated by centrifugation at 600 X g for 10 minutes. The supernatant was decanted, and the pellet was resuspended in 50 ml of normal saline" (col. 7, lines 18-20).

In sharp contrast, applicants' invention, as reflected by amended claim 1, claims a filtering step involving cross-flow filtration. Cross-flow filtration is used for concentration

adjustment of MVL, buffer exchange, and removal of unencapsulated drug. Cross-flow filtration for the preparation of MVL or liposomes give superior results over the previously described methods of buffer exchange, removal of unencapsulated drug, and concentration adjustment, such as centrifugation and decanting. Example 4 is a general example, showing the utility and advantages of cross-flow filtration, while Examples 13 and 15 provide illustration of the advantages of cross-flow filtration, particularly with respect to yield (an 8.4% improvement in overall yield; page 53, lines 6-7), and decreased process time (reduction from 50 minutes to 35 minutes; page 54, lines 17-19 and Fig. 22). Further, such methods of cross-flow filtration minimize the risk of a sterility breach. Particularly with respect to the process of claim 1, wherein all steps are to be carried out under aseptic conditions, this feature is highly important.

The prior art of record in this rejection does not appear to recognize this critical point, and discloses only methods of centrifugation and decanting in order to treat the compositions produced in those methods. The prior art of record in this rejection certainly does not teach any other method for the treatment of liposome or MVL compositions. Nor is there any suggestion or motivation for varying the disclosed methods. Since the cited prior art does not endeavor to carry out processes in which all steps are performed aseptically, there is no motivation for a method in which the risk of sterility breach is minimized. There is no suggestion that such a change from prior art processes would give any beneficial result.

The claimed invention is not obvious in light of the prior art of record, and applicants respectfully request reconsideration and withdrawal of the rejections.

Rejection Under 35 U.S.C. §103(a) Over Kim et al. (1987), Assil et al., Bonetti et al., Kim et al. '417, or Sankaram et al. Further in View of Kwasiborski et al. (United States Patent No. 6,033,708), Fenske et al. (United States Patent No. 5,837,282), Mehl Sr. et al. (United States Patent No. 5,885,260), Castor et al. (United States Patent No. 5,776,486), or Moynihan (United States Patent No. 5,589,189)

Claims 1-35, 48, 49 and 51 have been rejected as obvious over Kim et al. (1987), Assil et al., Bonetti et al., Kim et al. '417, or Sankaram et al., further in view of Kwasiborski et al., Fenske et al., Mehl Sr. et al., Castor et al., or Moynihan. Applicants respectfully traverse the rejections for the following reasons.

The additional references cited do not disclose the use of filtration steps in which cross-flow filtration is employed. Kwasiborski et al. discloses concentration by saying that "the solution is then passed through a series of filtration steps ending with the use of a filter that passes only particles having a size of about 0.2 μm in diameter (e.g., a 0.22 μm filter) to provide for a sterile solution of liposome encapsulated hemoglobin. Separation of unencapsulated hemoglobin could proceed with various separation method such as centrifugation, dialysis, filtration, column chromatography, followed by sterile filtration" (col. 5, lines 8-15).

The method of Kwasiborski et al. cannot be employed for the present invention, as the MVL particles of the present invention have a size in a range of, for example, from 13 to 18 microns (page 30, lines 23-25). This is because the particles are too large to pass through the filter, and materials intended to be separated from the particles cannot be separated by such filtration.

Fenske et al. discloses methods for loading a weakly basic drug into liposomes utilizing an electroneutral transport system. Thus, the method disclosed in this patent involves loading of preformed liposomes with pharmaceutically active substances. This is not at all analogous to the present invention, which instead operates by forming MVL with pharmaceutically active substances in place at the completion of MVL formation. As disclosed in Fenske et al., the replacement of the external solution can be accomplished by various techniques, such as, by passing the liposome preparation through a gel filtration column which has been equilibrated with a second aqueous buffered solution, or by centrifugation, dialysis, or related techniques" (col. 7, lines 46-50). Further, Fenske et al. notes that "[a] number of methods are available for the removal of ionophore from the liposome compositions including, for example, gel exclusion chromatography, dialysis, or treatment with biobeads" (col. 9, lines 59-62).

Mehl Sr. et al. discloses methods for the delivery of skin care products encapsulated in freeze-dried liposomes. It is disclosed in Mehl Sr. et al. that "liposomes spheres containing the encapsulated agent are then separated from the unincorporated agent by centrifugation or gel filtration" (col. 3, lines 51-53).

Castor et al. discloses methods for making liposomes containing hydrophobic drugs by means of supercritical fluid techniques. Although this reference does not generally appear to disclose filtration techniques, there is reference to the use of "gel-exclusion chromatography

(GEC) ... to separate unencapsulated taxoid from liposomes" (col. 23, lines 56-57). The distinctness of this reference in the method of preparation makes this reference inappropriate for comparison with the claimed invention.

Moynihan discloses a process for the production of a non-aggregating, filterable dispersion of liposomal encapsulated hemoglobin. Moynihan discloses "a series of filtration steps and with the use of a 0.45 micron filter and 0.2 micron filter to provide for a sterile solution of liposome encapsulated hemoglobin..." (col. 5, lines 48-50). As discussed with regard to Kwasiborski et al., such methods cannot be suitable for the preparations of particles having the large sizes of the present invention.

The cited prior art does not disclose the use of cross-flow filtration steps, used in a process which employs aseptic conditions throughout. There is no suggestion that such a filtration method would be suitable for the processes of the prior art. The claimed invention is not obvious over the cited prior art, and applicants respectfully request reconsideration and withdrawal of the rejections.

CONCLUSION

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Filed herewith is a check in payment of the excess claims fees required by the above amendments and Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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